ELSEVIER

• *CASE REPORT* •

Clostridium difficile causing acute renal failure: Case presentation and review

Jasmin Arrich, Gottfried H. Sodeck, Gürkan Sengölge, Christoforos Konnaris, Marcus Müllner, Anton N. Laggner, Hans Domanovits

Jasmin Arrich, Gottfried H. Sodeck, Marcus Müllner, Anton N. Laggner, Hans Domanovits, Department of Emergency Medicine, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, A-1090, Austria
Christoforos Konnaris, Department of Internal Medicine IV, Division of Occupational Medicine, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, A-1090, Austria
Gürkan Sengölge, Department of Medicine III, Division of Nephrology and Dialysis, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, A-1090, Austria
Correspondence to: Professor Hans Domanovits, Department of Emergency Medicine, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, A-1090, Austria, Europe
Telephone: +43-1-40400-1964   Fax: +43-1-40400-1965
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Abstract

AIM: *Clostridium difficile* infection is primarily a nosocomial infection but asymptomatic carriers of *Clostridium difficile* can be found in up to 5% of the general population. Ampicillin, cephalosporins and clindamycin are the antibiotics that are most frequently associated with *Clostridium difficile*-associated diarrhea or colitis. Little is known about acute renal failure as a consequence of *Clostridium difficile*-associated diarrhea.

METHODS: In this case report, we describe the course of *Clostridium difficile*-associated diarrhea in an 82-year-old patient developing acute renal failure. Stopping the offending agent and symptomatic therapy brought a rapid improvement of diarrhea and acute renal failure, full recovery was gained 18 d after admission. In a systematic review we looked for links between the two conditions.

RESULTS: The link between *Clostridium difficile*-associated diarrhea and acute renal failure in our patient was most likely volume depletion. However, in experimental studies a direct influence of *Clostridium difficile* toxins on renal duct cells could be shown.

CONCLUSION: Rapid diagnosis, nonspecific supportive treatment and specific antibiotic treatment, especially in the elderly, may lower excess mortality *Clostridium difficile*-associated diarrhea and renal failure being possible complications.

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INTRODUCTION

Clostridium difficile-associated diarrhea is more common in the hospital setting. A recent study found toxins of *Clostridium difficile* in 18% of inpatients and in 58% of inpatients with unexplained leukocytosis[1,2]. Overall mortality of patients with hospital-acquired *Clostridium difficile*-associated diarrhea was reported to be 15%[1]. However, toxins of *Clostridium difficile* have also been found out of hospital in 5% of fecal specimens of the asymptomatic general population[3]. Overall mortality of elderly patients admitted to an intensive care unit with the diagnosis of acute renal failure was reported to be 61%[4]. *Clostridium difficile*-associated diarrhea and acute renal failure are both well-recognized conditions but rarely occur together. The clinical course may be more severe and mortality increased particularly in the elderly population. Both conditions are reversible by relatively simple measures provided an early diagnosis is made. The clinical work-up and outcome of an 82-year-old man, suffering from acute renal failure due to preclinical-acquired *Clostridium difficile*-associated diarrhea, is presented. Epidemiology, diagnostics and standards of treatment are critically reviewed in line with current literature.

CASE REPORT

An 82-year-old man presented, in poor but stable general condition, to the local emergency department of a tertiary care university hospital with typical signs of gastroenteritis lasting for 5 d. His medical history included non-insulin-dependent diabetes mellitus since 10 years, two myocardial infarctions 1 year ago, cerebrovascular occlusive disease treated with carotid endarterectomy 2 years ago and pulmonary embolism 4 years ago. Initially, he had presented to his general practitioner with abdominal pain lasting for a few days. Considering his complex medical history his general practitioner put him on amoxicillin/clavulanate potassium. Because the symptoms did not improve during the following days and his general condition started to deteriorate, the patient called the ambulance and he was brought to the hospital. On examination the patient's blood-pressure was 115/85 mmHg (15/11 kPa), his pulse rate 60 beats/min, he was dehydrated but afebrile. Laboratory examinations showed highly elevated

plasma urea (41 mmol/L, normal range 2.5-6.7 mmol/L) and creatinine levels (1149.2 µmol/L, normal range 70-150 µmol/L) (Figure 1). Serum levels of electrolytes, white blood cell count and CRP were within normal range (CRP under 1 mg/dL, WBC 4.3-10.8×10⁹/L) (Figure 2), and fibrinogen was only slightly increased (6 g/L, normal range 1.80-3.90 g/L). Prerenal acute renal failure was assumed as primary working diagnosis because of dehydration due to prolonged diarrhea and the patient's long-term therapy with furosemide. Diuretics were stopped; under continuous intravenous and oral fluid replacement the patient's general condition improved. Prior to referral to a medical ward, stool cultures were requested. During the following days white blood cell count and acute phase proteins increased, indicating an ongoing infection. Chest x-rays showed no signs of pneumonia and blood cultures did not reveal bacteremia. Stool specimen was positive for *Clostridium difficile*. The patient was started on intravenous metronidazole 1.5 g/d. Three days after onset of specific therapy, inflammatory markers reached maximum levels (WBC 12 g/L, CRP 6 mg/dL) and decreased in the further course (Figure 2), while plasma urea and creatinine levels returned to normal (Figure 1). *Clostridium difficile* toxins could not be detected in any subsequent stool samples. Fully recovered, the patient could be discharged from hospital, 18 d after initial presentation.
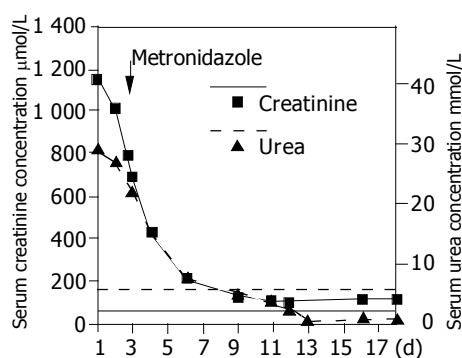

Figure 1 Serum urea (---) and creatinine (—) levels over time of hospital stay with the horizontal lines representing normal ranges of urea (---) and creatinine (—). The arrow indicates start of specific antibiotic treatment.
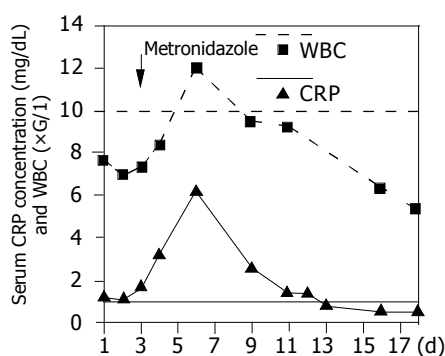

Figure 2 White blood cell count (---) and serum CRP levels (—) over time of hospital stay with horizontal lines representing normal ranges of white blood cell count (---) and CRP (—). The arrow indicates start of specific antibiotic treatment.

DISCUSSION

Risk factors

Considering the high prevalence of *Clostridium difficile* infections in the hospital setting, our patient may have been infected during a previous hospital stay. But an acquisition of infection out of hospital is not excluded. Because of his old age and his comorbidities including non-insulin-dependent diabetes mellitus, ischaemic heart disease, cerebrovascular occlusive disease and pulmonary embolism, he certainly was at risk to develop *Clostridium difficile*-associated diarrhea as well as acute renal failure. Antibiotic-associated diarrhea as a common course of infection with *Clostridium difficile* has a broad spectrum of clinical manifestations ranging from mild diarrhea to pseudomembranous colitis and fulminant colitis[5]. The risk factors that could be identified as associated with severe disease (defined by a hospital stay of greater than 14 d, colectomy, intensive care unit admission or death of patient) were age over 70 years, comorbid illnesses, and recurrence of *Clostridium difficile*-associated diarrhea[6]. Acute renal failure is characterized by an abrupt decline in renal function resulting in an inability to excrete metabolic wastes and maintain proper fluid and electrolyte imbalance[7]. Prerenal acute renal failure together with intrarenal acute renal failure due to ischaemia and nephrotoxins are responsible for most episodes of acute renal failure[8]. Common causes of prerenal failure are volume depletion as a result of diarrhea, reduced fluid intake, fever, diuretics, or heart failure. Elderly patients are particularly susceptible to prerenal failure because of their predisposition to hypovolaemia and high prevalence of renal-artery atherosclerotic disease[9].

Developments of the diagnosis of Clostridium difficile-associated diarrhea

The diagnosis of *Clostridium difficile*-associated diarrhea was confirmed by ELISA testing for enterotoxin A and B. The diagnosis of an infection with *Clostridium difficile* can be made either by testing for toxin A or B (ELISA and cytotoxin assay), bacterial enzymes (Latex agglutination test) or by bacterial culture. Bacterial culture is highly sensitive and allows bacterial strain typing, but also takes 2-5 d to perform[5]. Latex agglutination tests are fast and inexpensive and have improved in sensitivity in the past few years[10].

Treatment

For our patient, intravenous and oral fluid replacement therapy in addition to the appropriate antibiotic agent brought a rapid improvement in his condition. In fact both diseases share the same principles of nonspecific treatment (Table 1, 2). Reversing the underlying cause is the first and most beneficial measure. In *Clostridium difficile* infection it is discontinuation of offending antibiotic treatment, in acute renal failure it may be stopping a nephrotoxic agent or treating diarrhea. Further important measures in both diseases are replacing intravascular volume and correcting electrolyte abnormalities.

Clostridium difficile and antibiotics

In our case, amoxicillin/clavulanate potassium seemed to have initiated deterioration of first mild gastrointestinal symptoms. The development of *Clostridium difficile*-associated diarrhea and pseudomembranous colitis, however, is not

restricted to certain antibiotics. The ones that are most frequently associated are ampicillin, cephalosporins and clindamycin. If patients require antibiotics, another way of treating them is changing to an agent that has less frequently been associated with the disease[5]. First line agents for the treatment of symptomatic *Clostridium difficile* infection include oral vancomycin or metronidazole. A recent study, investigating resistance of *Clostridium difficile* strains to different antibiotics found no evidence that the most common human strains were resistant to vancomycin or metronidazole while all strains were resistant to cefoxitin and most strains resistant to ceftriaxon[11].

Table 1 Treatment of acute renal failure[7]

Reverse underlying causes
Return intravascular volume and mean arterial pressure to normal
Correct electrolyte imbalances
Treat hyperkalaemia and acidosis with inhaled beta-agonists, insulin/glucose, sodium bicarbonate, binding resins (sodium polystyrene sulfonate)
Discontinue or avoid nephrotoxins
Adjust doses of medications that are eliminated by the kidney or by dialysis
Initiate renal replacement therapy in case of volume overload, hyperkalaemia, metabolic acidosis refractory to medical treatment
Obtain nephrologic consultation as soon as possible

Table 2 Treatment of infections with toxigenic *C. difficile*[5]

Discontinuation of offending antibiotic
Correction of fluid loss and electrolyte imbalance
Antimicrobial agents if symptoms are severe or persistent
Oral agents (preferred)
Metronidazole: 250 mg, four times daily to 500 mg 3 times daily for 7–14 d
Vancomycin: 125 mg, four times daily, 7–14 d
Parenteral agent
Metronidazole: 500 mg, given intravenously every 6 h

More than volume depletion?

In our case the most likely link between *Clostridium difficile* colitis and acute renal failure was volume depletion due to prolonged diarrhea. Dramatic improvement of the patient's general condition and rapidly decreasing serum creatinine and urea levels after initiation of fluid therapy support this hypothesis. A medline search retrieved three articles dealing with acute renal failure in patients with *Clostridium difficile*-associated diarrhea. Two articles reported on hospitalized patients with acute and chronic renal failure developing *Clostridium difficile*-associated diarrhea[12,13], another one described a case of IgA nephropathy after out of hospital acquired antibiotic-associated *Clostridium difficile* colitis[14]. As potential cause the authors discuss an immunologic perturbation, culminating in mesangial IgA deposition. In our case no renal biopsy was taken, however, an IgA nephropathy as underlying cause of acute renal failure was not likely. Mere experimental are influences of *Clostridium difficile* toxins on renal duct cells. Klussmann and Maric reported that *Clostridium difficile* toxin B increases water permeability in primary cultured collecting duct cells by translocating aquaporin-2 water channel carrying vesicles into the cell membrane[15]. Cell death cells plays a major role in acute renal failure and it could be observed that toxins of *Clostridium difficile* initiate. Whether these mechanisms contribute to acute renal failure remain to be investigated.

In conclusion, our patient presented with a course of *Clostridium difficile*-associated diarrhea followed by acute renal failure. Under continuous volume replacement therapy and specific antibiotics the patient's general condition improved, inflammatory markers, serum urea and creatinine rapidly returned to normal and the patient could be discharged after full recovery 18 d after admission. Both acute renal failure and *Clostridium difficile*-associated diarrhea are potentially life-threatening diseases in the elderly but may be reversed using appropriate therapy. Keeping in mind a possible direct link between these two serious diseases, this report once more stresses the need for rapid diagnosis and specific treatment, especially in the elderly, to prevent fatal outcome.

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